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Ultrasound detected inflammation is associated with the development of new bone erosions in hand osteoarthritis: a longitudinal study over 3.9 years

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SUMMARY

Objective: To evaluate the association between ultrasound (US) detected inflammation at baseline and the subsequent development of new bone erosions at follow-up in patients with hand osteoarthritis (HOA).
Method: 32 of the 35 (10 controls, 12 patients with non erosive HOA (non-EHOA), 13 with EHOA subjects originally studied were re-evaluated 3.9 years after the initial study, by means of standard radiography and US examination. Kellgren–Lawrence (K-L) and Kallman scores were utilized to evaluate 576 interphalangeal (IP) joints. US detected synovial inflammation features were scored as present/absent. US detected bone erosions were also investigated. The association between synovial inflammation features at baseline and the development of new bone erosions was evaluated using the generalized linear mixed model (GLMM) after adjustment for patient effect, age, gender, body mass index.
Results: In HOA patients, radiographic scores worsened and bone erosions progressed. In HOA patients similar percentages of joints with Power Doppler Signal (PDS) and gray scale (GS) synovitis were found comparing baseline and follow-up examinations, whilst a significant increase was found in the joints with effusions. Only a minority of joints were positive on both occasions (between 2 and 6 %), the majority fluctuated between positive and negative and vice versa. PDS positivity was associated with new radiographic central erosions and US-detected bone erosions, whereas GS synovitis and effusion were not.
Conclusions: Radiographic scores and bone erosions increased over a period of about 4 years. Synovial inflammation as detected by PDS was associated with the appearance of new bone erosions.

Introduction

The hand is one of the most common sites of osteoarthritis. The clinical form has a prevalence of about 20% in people aged 65 years and over[1] and a higher prevalence (80% in the elderly population) can be seen if radiographic definition alone is taken into account[2]. Hand osteoarthritis (HOA) is a leading cause of disability of the hands: this disability is more pronounced if severe involvement of the first carpo-metacarpal joint (CMC1) is present or if severe radiographic changes, called central erosions, are detected in the distal and proximal interphalangeal joints (DIP/PIP)[3–6]. The latter form of HOA is called erosive or inflammatory, since it is characterized by episodes of swelling and tenderness (sometimes associated with redness) and acute pain in one or more IP joints[7,8]. Central erosions are areas of subchondral bone collapse in the central zone of the joint, without clear evidence of central bone breaks.

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A considerable number of people with HOA will develop the erosive disease, which can appear at variable time intervals from the diagnosis of HOA[5,9–11]. The association of bone erosions and the presence of inflammation, both clinically and at US examination, has led to the suggestion that bone damage may be induced by synovitis, as seen in Rheumatoid Arthritis (RA). Indeed, the erosive disease does not appear to be a distinct entity from the non erosive form, since the joint topography of the structural damage[12,13] and the presence of systemic complications (hypertension, dyslipidemia, autoimmune thyroiditis) are similar in both forms[14,15], though this remains a matter of debate.

We, and others, have demonstrated that US-detected synovitis (GS synovitis), effusion and PDS are frequently observed in erosive HOA (EHOA), particularly, but not exclusively, in joints with central erosions[16–20].

To date, the majority of studies carried out on US-detected synovitis and structural damage in HOA have been cross sectional[16–20], therefore unable to evaluate the association between synovitis and the progression of damage, along the lines of what has already been soundly demonstrated in patients with RA, both at patient and joint levels[21]. Not long ago, two longitudinal studies carried out by the same group assessed the role of synovial inflammation in the appearance of new structural damage and pain in HOA patients[22,23] Hence, we performed a longitudinal prospective study evaluating the US inflammatory (synovitis) features and radiographic US-detected bone erosions in a series of subjects, including cases with either no clinical or X-ray HOA or with non erosive and erosive forms of HOA.

The primary evaluation of this series of subjects has already been reported[17]. The same subjects were then re-evaluated after an average of 4 years, when we considered the relationship between the US features of synovial inflammation at baseline and new bone erosions detected after this 4-year period (follow-up).

Patients and methods

Patients

We performed an X-ray and US re-evaluation of the 35 cases from the original study (Baseline, 10 controls without joint disease, 12 patients with non erosive HOA and 13 with EHOA). Consecutive patients affected by HOA according to the ACR classification criteria[24] were recruited in our rheumatology outpatient clinic. Patients with erosive disease were identified by conventional radiology (i.e., by the presence of the classic central erosion patterns – gull-wing or saw-tooth appearance-in at least two joints). Control subjects were randomly selected from people attending our outpatient clinic for minor, non-specific complaints: these subjects had no finger joint pain and/or tenderness and no finger nodes; therefore they were classified as clinically normal controls (NC). Exclusion criteria were: trauma to or operation on the hands during the 6 months, or an intra-articular injection during the 3 months prior to inclusion, the assumption of oral corticosteroids 1 month prior to inclusion. People with positive rheumatoid factor or psoriasis or a history of psoriasis in first degree relatives were excluded. In addition, subjects with signs or symptoms suggestive of connective tissue disease, other inflammatory arthritides or inflammatory bowel diseases were also excluded from the study. Finally, a history or imaging suggestive for gout and chondrocalcinosis (calcium pyrophosphate deposition disease) were also considered as exclusion criteria. All patients and NC gave written informed consent and approval from the ethics committee of our institution was obtained. The second imaging study was performed after 3.9 years (Mean ± SD: NC = 3.88 ± 0.38; non-EHOA patients = 3.96 ± 0.29; EHOA patients = 3.95 ± 0.33). Three subjects (1 normal control, 2 non erosive HOA patients) were lost to follow up: one refused to be re-evaluated and two moved away. None of the studied cases received corticosteroid treatment (oral, parenteral or intrarticular) for any reason during the follow-up period.

Radiographs

Posterior-anterior radiographs of both hands of the 32 subjects were obtained within a maximum of 3 weeks from the US examination and the radiological involvement of the single joints was graded according to the K&L and Kallman scoring systems[25–27]. We evaluated the 18 interphalangeal (IP) joints of each patient. Results of K&L and Kallman scores are given either per joint or per patient: the evaluated items in Kallman score were osteophytes (0–3), joint space narrowing (0–3), subchondral cysts (0–1), subchondral sclerosis (0–1), lateral bony deviation ($\geq 15^{\circ}$; 0–1), and cortical collapse (0–1). Score range: per joint K&L 0–4, Kallman 0–10. We evaluated the presence of bone erosions: central bone erosions (CE) characterized by the classic gull-wing and saw-tooth patterns and marginal bone erosions with cortical bone breaks localized between the edge of the articular cartilage and the joint capsule.

All the images were blinded for identifying data and time sequence; the radiological scoring was performed in random order by a rheumatologist (O.A.) with experience in hand radiological scoring. She evaluated all the X-ray films and DVDs, unaware of the US findings. The intra-reader variability was obtained on the re-examination of 15 randomly selected radiographs. The ICC values for intra-reader reliability for single joint K&L and Kallman scores were excellent: 0.99 (0.99–0.99) for K-L, and 0.91 (0.850–0.96) for the Kallman score.

Ultrasound (US) procedure

US joint examination was performed using light pressure and a large quantity of visible scanning gel between the transducer and the skin. Patients were in a comfortable position with their hands completely relaxed in order to avoid movement artifacts and with the finger joints in a neutral position, but extended and flexed as required for the visualization of pathology. We used the same model (Acuson Antares Siemens apparatus) and machine setting (11.4 MHz, 30 dB/DR60, MapE/VEOff, RS3/SCOff) for all patients and controls. Longitudinal and transverse US examination was performed on both hands on the volar and dorsal sides using a multifrequency linear transducer (VFX 13e5 MHz, 18 fps; TIS 1.2/TIB 1.2). Measurements were conducted to the depth of 20 mm. Power Doppler settings were standardized with a lower pulse repetition frequency (305 MHz) and a Doppler frequency of 8 MHz; wall filters were set at the lowest value (F1). Colour priority was maximized to evaluate vessels that were not visible on GS. We set the colour gain by turning up the Doppler gain until random noise was encountered and then it was lowered until the noise disappeared (3–4 dB). A total of 576 joints were examined: proximal interphalangeal (PIP) 1–5 and distal interphalangeal (DIP) 2–5 joints. Indicators of synovial inflammation were: 1) PDS, defined as a signal within a region of GS synovitis, was assessed as present/absent (since only a small minority of PDS positive joints score 2 plus and none 3 plus)[28] 2) synovial thickening - GS synovitis (present/absent), 3) joint effusion (present/absent) [using the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definitions developed for RA][28]. Structural pathology was investigated by evaluating the presence of erosions (an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes on imaging)[28]. Joints with ankylosis were excluded from US evaluation. US

examination was performed by two experienced musculoskeletal ultrasonographers (LM and PP) blinded to patient radiographic data. They scored together each US feature and always gave a consensus result. Intra-observer variability was tested by performing a second US in 15 randomly selected subjects, 1 week after the first US evaluation.

The intra-observer variability depicted by *k* coefficient was 0.83 (95% CI: 0.75–0.90) for effusion, 0.84 (95% CI: 0.76–0.93) for synovial thickening, 0.78 (95% CI: 0.68–0.89) for PDS and 0.87 (95% CI: 0.81–0.93) for bone erosions.

In our first article[17], we did not report two of the imaging features which were examined at that time: radiographic marginal bone erosions and US-detected bone erosions. Here, we report both the first and second evaluation of these two additional features.

In order to evaluate the time relationship between the presence of synovitis features at baseline and the development of new bone erosions at follow-up, we only took into consideration the joints which were without bone erosions at baseline and compared the percentage of joints with new erosions at follow-up in the two groups of joints, with and without US inflammatory features at baseline.

Statistical analysis

Statistical analysis was performed using the standard software packages SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and the SAS System for Windows release 8.0.

The assumption of our work was that the synovitis should herald new bone erosion adjusted for confounding effects from sex, age, BMI and patient.

The Dependent variables consisted in N trials (joints) assuming two possible values: erosion or not erosion (Bernoulli random variables): we were interested in the response in the form of proportions of erosions (binomial distribution) obtained when a group of N individuals are exposed to the same conditions.

The analysis of the increase of joint erosions was carried out utilizing the generalized linear mixed model (GLMM) with binomial distribution for dicotomic variables. Patient and gender were considered as random effects and BMI and age were considered as covariates. The adjusted values were expressed as a percentage and 95% CI.

For the evaluation of the association between baseline US inflammatory features and follow-up bone erosions, new central and marginal radiographic erosions and new US erosions were defined as dependent variables with binomial distribution. The analysis of joint erosions was carried out utilizing the GLMM with binomial distribution with log link function. The risk factors (PDS, joint effusion and GS synovitis) were separately evaluated and were considered as fixed effects. The influence of the risk factors was adjusted considering patients and gender as random effects and BMI and age as covariate. Therefore the dependent variables were expressed as percentages and 95% CI.

Two-sided probability values of <0.05 were considered to be statistically significant.

Results

Changes in radiographic and US findings between baseline and follow-up examination

The demographic data of the patients are reported in Table I.

In NCs, the increase in bone erosions from baseline to follow-up was negligible (CE: 0 to 1, ME: 1 to 2, US-E: 7 to 10). In addition, US inflammatory features both at baseline and follow-up also occurred in a small number of joints (PDS = 1 to 1, GS synovitis = 14 to 12, effusions = 12 to 11).

In HOA patients, both the K-L and Kallman scores worsened. Indeed, the number of joints with a K-L score ≥ 2 increased in all three groups of subjects (Table I).

In HOA patients, the percentages of joints with bone erosions significantly increased (Table II). Similar percentages of joints with PDS and US synovitis were found in HOA patients when baseline and follow-up examinations were compared (PDS from 10.1% to 10.6%, GS synovitis from 13.3% to 12.3%) whilst a significant increase was found in the number of joints with effusions (from 13.0% to 26.2%) (Fig. 1). We did not find a significant preferential localization of US inflammatory features either in PIP or DIP joints both at baseline and follow-up (data not shown). In Fig. 2, the evolution of US finding in a PIP joint of a HOA patient is shown. In HOA patients, only a small minority of joints was positive both at baseline and at follow-up (PDS = 2.2%, GS synovitis 2.7%, effusion 5.9%). Indeed, the majority of positive joints at baseline became negative

Table I
Patient demographic and radiographic data. Radiographic scores are expressed per joint

	NC	Non-EHOA	EHOA
Demographic data *(Baseline)*			
Women, % (*n*)	80 (8)	83 (10)	100 (13)
Age (yrs), mean ± SD (95% CI)	66.8 ± 9.0 (60.3–73.3)	67.0 ± 7.5 (62.2–71.8)	63.9 ± 8.2 (59.0–68.9)
Disease duration (yrs), median (25°–75° percentiles)	–	6 (3–13)	7 (4–13)
BMI, mean ± SD (95% CI)	24.9 ± 3.4 (22.5–27.3)	25.8 ± 4.7 (22.8–28.7)	25.2 ± 2.9 (23.4–26.9)
Radiographic scores			
Baseline	$n = 10$	$n = 12$	$n = 13$
K&L, mean ± SD (95% CI)	0.77 ± 0.65 (0.69–0.86)	1.27 ± 0.90 (1.16–1.38)	1.75 ± 1.29 (1.61–1.88)
K&L ≥ 2, *n* of joints (%)	28 (17%)	76 (42%)	169 (72%)
Kallman, mean ± SD (95% CI)	3.15 ± 1.39 (2.94–3.37)	4.41 ± 1.94 (4.13–4.70)	5.75 ± 2.56 (5.45–6.04)
Osteophytes, mean ± SD (95% CI)	0.90 ± 0.53 (0.81–0.98)	1.33 ± 0.73 (1.22–1.43)	1.57 ± 0.89 (1.46–1.69)
JSN, mean ± SD (95% CI)	0.88 ± 0.58 (0.79–0.97)	1.41 ± 0.75 (1.30–1.52)	1.71 ± 0.85 (1.60–1.81)
Follow up	$n = 9$	$n = 10$	$n = 13$
K&L, mean ± SD (95% CI)	0.79 ± 0.67 (0.71–0.87)	1.41 ± 1.02 (1.29–1.53)	1.85 ± 1.29 (1.71–1.98)
K&L ≥ 2, *n* of joints (%)	30 (19%)	87 (48%)	184 (78%)
Kallman, mean ± SD (95% CI)	3.21 ± 1.43 (2.99–3.43)	4.74 ± 2.18 (4.41–5.06)	6.00 ± 2.33 (5.70–6.31)
Osteophytes, mean ± SD (95% CI)	0.91 ± 0.51 (0.80–0.97)	1.42 ± 0.90 (1.30–1.49)	1.81 ± 1.20 (1.76–2.20)
JSN, mean ± SD (95% CI)	0.90 ± 0.59 (0.77–0.99)	1.47 ± 1.0 (1.31–1.53)	1.76 ± 1.0 (1.51–1.88)

Table II
Percentages (95% CI) and numbers, in square brackets, of joints with bone erosions: progression during follow up in HOA patients (Total joints = 414)

	CE	ME	US-E
Baseline	12.1 (8.9–15.4), [49]	22.1 (18.0–26.3), [88]	7.0 (4.4–9.5), [33]
Follow-up	18.3 (14.5–22.2), [74]	58.3 (53.4–63.3), [237]	41.5 (36.7–46.2), [166]
P-value*	<0.001	<0.001	<0.001

CE = radiographic central erosions; ME = radiographic marginal erosions; US-E = ultrasonographic erosions.
* GLMM with binomial distribution corrected for patient, age, sex, BMI.

at follow-up and, conversely, the vast majority of positive joints at follow-up were negative at baseline (Fig. 1).

Association between US findings at baseline and new bone erosions at follow-up

Given the low number of bone erosions and the low number of joints with US inflammatory features, we did not include NC joints in the comparison between US features at baseline and new bone erosions at follow-up.

In order to evaluate the association between US findings at baseline and newly developed bone erosions, we only took into consideration HOA patient joints without bone erosions at baseline: for central erosions 356 joints, for marginal erosions 314 joints, for US-detected erosions 371 joints.

We found that the presence of PDS was significantly associated with a higher prevalence of new CE, the strongest association being found in PIP joints (Supplementary File 1) No association was observed between the presence of GS synovitis or effusion at baseline and the development of new CE at follow-up (Table III).

No significant association was found between PDS, GS synovitis and effusion at baseline and the development of new marginal bone erosions at follow-up.

Finally, a significant association between PDS positivity and new US detected bone erosions was found. The strongest association was found in DIP joints (Supplementary File 1). Again, no association was found when GS synovitis and effusion were taken into consideration (Table III).

Nonetheless, taking into consideration the absolute number of joints with new erosions, the vast majority of newly developed erosions occurred in joints without inflammatory features in baseline (Table III).

Discussion

In this study, the bone erosions found in the non-EHOA and EHOA patient groups significantly progressed during the time lag between baseline and follow-up. Since new structural damage was added at follow-up, it was feasible to look for an association between US detected inflammatory features at baseline and the newly developed bone erosions. Several papers report that new significant damage in HOA can be accrued over a period of between 1 and 10 years, many reports dealing with an interval of 2–6 years[9,29–33].

US inflammatory features, both at baseline and follow-up, affected only a minority of joints. In addition, they showed great variation in topography: this phenomenon can be related to a) the fluctuating inflammatory disease in different joints of HOA, as recently demonstrated in a short (3-month) follow up study[22], b) the long time lag between the first and second imaging studies,

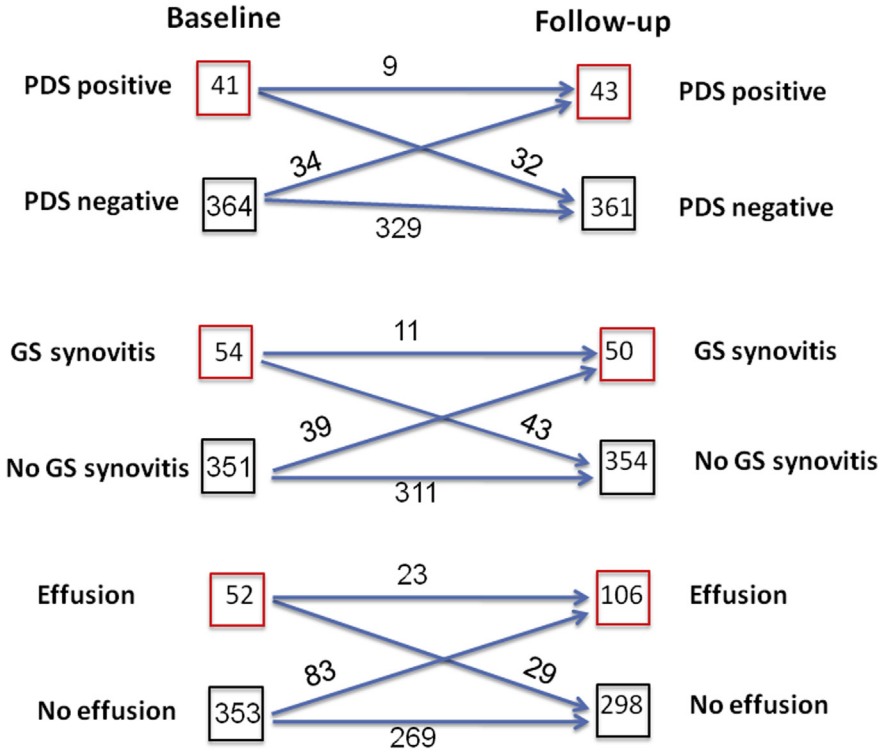

Fig. 1. Distribution of inflammatory US features in the joints of HOA patients studied at baseline and follow-up and their changes over 3.9 years of follow up.

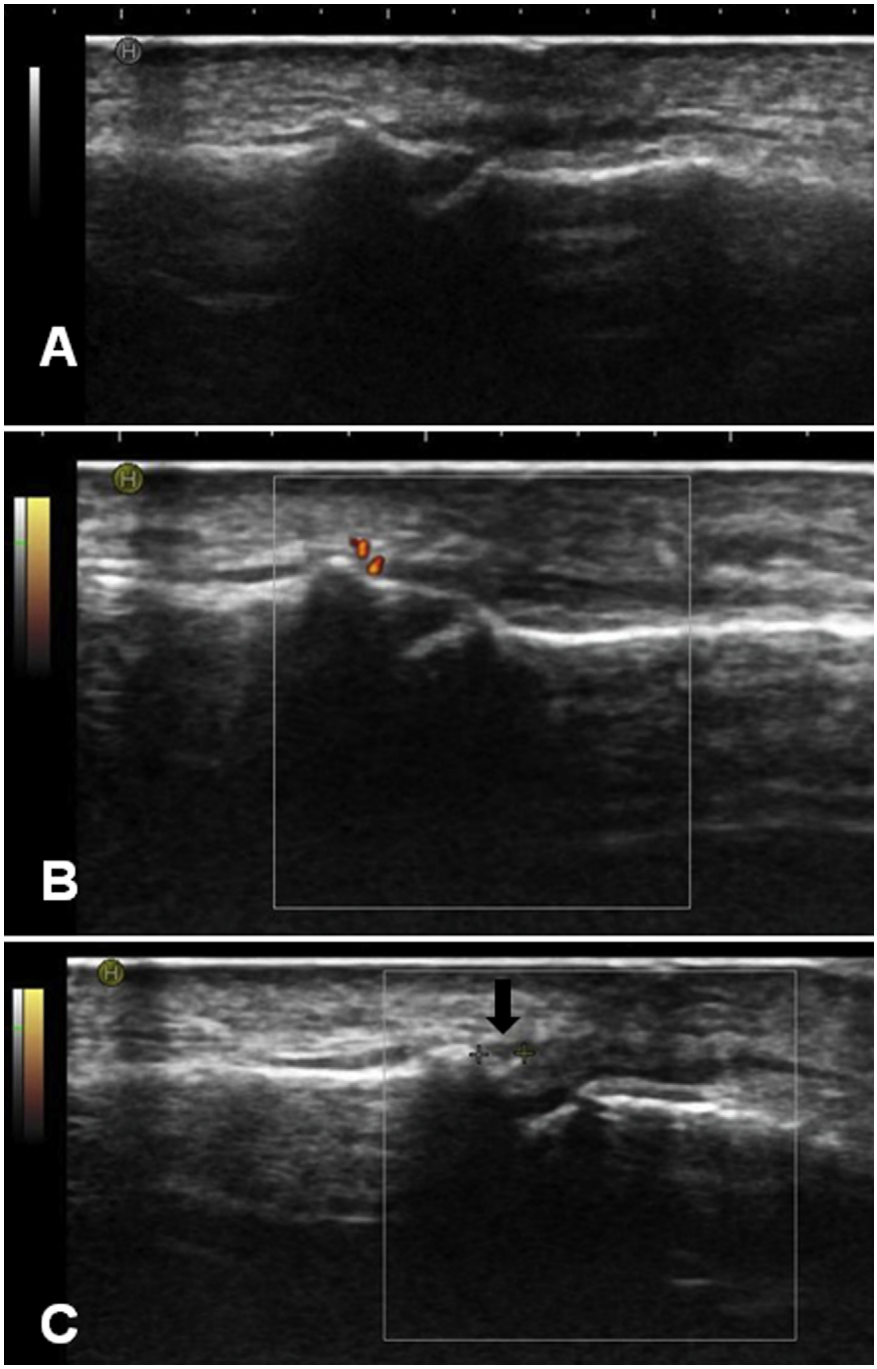

Fig. 2. Longitudinal US image of the second left PIP joint. A. Baseline: grey scale synovitis, no bone erosion. B. Baseline: presence of PDS. C. Follow up: presence of new bone erosion and absence of PDS. Arrow: bone erosion.

with the consequent possibility of spontaneous remissions and flares of joint inflammation[22]

This is the first long-term longitudinal study addressing the role of synovial inflammation and the development of bone erosions in HOA.

Only PDS was found to be associated with subsequent new CE and new US erosions, but not with new radiographic marginal erosions. Therefore, synovial inflammation could represent one mechanism leading to erosive disease, even if the other inflammatory features (GS synovitis and effusion) were not associated with newly developed erosions of any kind. In addition, taking in consideration the absolute number of newly developed erosions, we found the vast majority of erosions occurred in joints without inflammation at baseline, thus underlining the relative role of inflammation in the pathogenesis of bone erosions in HOA.

Indeed, the role of synovial inflammation in the pathogenesis of bone erosions and joint structural derangement is well established in RA[34–36] and in spondyloarthritis the role of enthesis inflammation is also acknowledged[36–38]. But in these inflammatory arthritides, synovial inflammation is much more frequent (almost always present) than in HOA. Therefore, the mismatch between the frequency of synovial inflammation (low) and occurrence of bone erosions (high) in HOA, may explain our absolute number findings.

Table III
Association between inflammatory ultrasound features at baseline and the development of new bone erosions at follow-up (expressed as percentage of positive and negative joints [% (95% CI)]).

US inflammatory features at baseline		PDS			GS synovitys			Effusion		
		Positive	Negative	p^	Positive	Negative	p^	Positive	Negative	p^
New bone erosions developed at follow up	*CE	15.9 (3.0-28.8)	6.2 (3.6-8.8)	**0.048**	6.3 (0-13.8)	7.1 (4.3-10.0)	0.846	3.2 (0-28.7)	3.5 (0-9.9)	0.970
	n° of joints with new CE/total n°	5/31	20/325		3/46	22/310		3/44	22/312	
	°ME	62.2 (42.6-81.9)	46.2 (40.4-51.9)	0.123	54.6 (39.4-69.9)	46.3 (40.4-52.3)	0.320	56.9 (41.4-72.5)	46.1 (40.2-52.0)	0.202
	n° of joints with new ME/total n°	16/25	133/289		22/42	127/272		22/40	127/274	
	#US-E	58.4 (43.6-73.2)	33.3 (28.4-38.3)	**0.002**	35.1 (22.1-48.1)	36.0 (30.9-41.1)	0.903	36.9 (23.7-50.1)	35.7 (30.6-40.8)	0.870
	n° of joints with new US-E/total n°	21/37	112/334		19/50	114/321		19/48	114/323	

We assessed 405 out of 414 joints (9 were excluded for ankylosis), but for each analyses we omitted joints that at baseline presented the type of erosion examined, in particular: *49 joints (12.1%) had CE, assessed 356 joints; °88 joints (21.7%) had ME, assessed 317 joints; #33 joints (8.1%) had US-E, assessed 372 joints.

^ GLMM with Loglinear Binomial Distribution univariate analysis corrected for patient, age, sex, BMI.

PDS: Power Doppler Signal; GS: Gray Scale; CE: Radiographic Central Erosion; ME: Radiographic Marginal Erosion; US-E: ultrasonographic erosions.

Bone erosions can frequently be detected (by conventional radiology, magnetic resonance imaging- MRI, US) in HOA[39], but their pathogenesis has not been thoroughly investigated or well defined[40–42]. In addition, the central erosions which characterize the erosive subset of HOA are probably not true erosions (with bone cortical break) but rather a bone attrition phenomenon (bone collapse)[43]. The lack of time association between PDS and radiographic marginal erosions casts doubt on a direct causative role of synovial inflammation in bone and cartilage damage in HOA, in contrast to what is seen in inflammatory hand arthritis[21,44]. That being said, we must be cautious in our interpretation of the facts. Firstly, only a minority of joints were positive for synovial inflammation both at baseline and follow-up, whilst the majority of joints had cartilage and/or bone damage: therefore, synovial inflammation is much rarer than other types of damage[45,46].

Secondly, inflammation features and, in particular, PDS are much rarer and milder in HOA than in RA and fluctuate widely[22]. In our patients, PDS almost always scored 1 plus, rarely 2 plus. It is noteworthy that the prognostic value of PDS positivity in single joint damage progression in RA has been confined to 2–3 plus PDS positivity[21]. This data has also been recently confirmed in patients with HOA, even if related to osteophyte and joint space narrowing progression[23].

Thirdly, the time lag between the first and second evaluations is much longer than in previous RA studies[21,47]. Therefore, the link between the inflammatory features at baseline and the erosions at follow-up, even when observed, is certainly debatable.

While in RA, inflammation is a major driving force behind joint damage, in OA, other mechanisms may play a major role and, in particular, biomechanical stimuli can arguably simultaneously elicit molecular changes in cartilage and bone and inflammation in synovium, thus coupling inflammation and structural damage[48,49]. This hypothesis was indirectly confirmed by our previous finding of a strong association of PDS positivity with CE and worse K-L and Kallman scores in a cross sectional study[17]. In addition, in recent years, the McGonagle group, utilizing elegant MRI studies, has suggested that enthesitis/osteitis plays a role in the development of structural damage in IP joints in HOA, in a similar way to what happens in IP psoriatic arthritis[50].

Finally, our study has some weaknesses. The sample size of our series is certainly limited and this is related to the number of patients originally studied[17]. However, we evaluated all the IP joints of our patients, therefore we believe that the number of joints studied is enough to show a trend. Furthermore, the duration of follow-up (almost 4 years) without an intermediate US evaluation certainly weakens the association between inflammatory features at baseline and bone erosions at follow-up.

In conclusion, we observed, for the first time, an association between US-detected synovial inflammation (PDS) and the development of new bone erosions in HOA. The pathogenic significance of this association should be addressed in further studies with larger study populations and with multiple evaluation checkpoints.

Authors' contributions

LM: conception and design, data collection and analysis, interpretation of data, manuscript writing and final approval of the manuscript.

OA: data collection and analysis, interpretation of data, manuscript writing contribution and final approval of the manuscript.

EP: statistical analysis, manuscript drafting contribution and final approval of the manuscript.

LP: conception and design, statistical analysis, manuscript writing and final approval of the manuscript.

RM: conception and design, critical revision, manuscript writing, final approval and take responsibility of the manuscript.

All authors read and approved the final manuscript.

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Competing interest statement

The authors declare that they have no competing interests.

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Supplementary data

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